Chapter 5

EXOSOMES DERIVED FROM HUMAN UMBILICAL CORD MESENCHYMAL STEM CELLS (hUC-MSCs) IN CELLULAR EXPERIMENTS AND THERAPEUTICAL APPLICATION ON ANIMAL

Ferda TOPAL CELİKKAN[1]

The Characteristic of Human Umbilical Cord Derived Mesenchymal Stem Cells (hUC-MSCs)

Mesenchymal stem cells can be extracted from many sources [(1)]. Human umbilical cord is one of them, which can be obtained and produced from many different parts of the structure and it exists from perivascular region to amniotic epithelium. It is known as human umbilical cord derived mesenchymal stem cells (hUC-MSCs). A small number of stroma cells are found in a highly intercellular fluid, along with thin and scattered collagen fiber bundles in the Wharton Jelly. As the umbilical cord is thrown away after birth, invasive intervention does not necessitate and the ethical difficulty are not present [(2)]. Since isolation of hUC-MSCs, these cells have been strikingly characterized and identified. The interest in these cells is increasing in last decade and it is revealed that it has therapeutic effectiveness [(3)]. hUC-MSCs like mesenchymal stem cells have broad prospects for regenerative medicine, which principally because of their self-renewal, differentiation potential to three lineages as adipogenic,

[1] Assistant Professor, Ankara University, Faculty of Medicine, Department of Histology and Embryology, ferdatopal@gmail.com

CONCLUSION

The exosomes therapies which is a cell-free treatment have significant impact on different pathologic condition. HUC-MSCs derived exosomes hold great promise for applying in clinical trials using their paracrine and therapeutic effects. The exact molecular mechanisms concerning effect roles of hUC-MSC exosomes need to be enlighten. The cellular and animal studies help the improvement of the clinical researches and require further investigations.

REFERENCES

1. Hass, R., C. Kasper, S. Bohm, and R. Jacobs, *Different populations and sources of human mesenchymal stem cells (MSC): A comparison of adult and neonatal tissue-derived MSC.* Cell Commun Signal, 2011. **9**: p. 12.
2. Bharti, D., S.B. Shivakumar, J.K. Park, I. Ullah, R.B. Subbarao, J.S. Park, S.L. Lee, B.W. Park, and G.J. Rho, *Comparative analysis of human Wharton's jelly mesenchymal stem cells derived from different parts of the same umbilical cord.* Cell Tissue Res, 2018. **372**(1): p. 51-65.
3. Davies, J.E., J.T. Walker, and A. Keating, *Concise Review: Wharton's Jelly: The Rich, but Enigmatic, Source of Mesenchymal Stromal Cells.* Stem Cells Transl Med, 2017. **6**(7): p. 1620-1630.
4. Karahuseyinoglu, S., O. Cinar, E. Kilic, F. Kara, G.G. Akay, D.O. Demiralp, A. Tukun, D. Uckan, and A. Can, *Biology of stem cells in human umbilical cord stroma: in situ and in vitro surveys.* Stem Cells, 2007. **25**(2): p. 319-31.
5. Park, K.S., E. Bandeira, G.V. Shelke, C. Lasser, and J. Lotvall, *Enhancement of therapeutic potential of mesenchymal stem cell-derived extracellular vesicles.* Stem Cell Res Ther, 2019. **10**(1): p. 288.
6. Phan, J., P. Kumar, D. Hao, K. Gao, D. Farmer, and A. Wang, *Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy.* J Extracell Vesicles, 2018. **7**(1): p. 1522236.
7. Li, D., D. Zhang, B. Tang, Y. Zhou, W. Guo, Q. Kang, Z. Wang, L. Shen, G. Wei, and D. He, *Exosomes from Human Umbilical Cord Mesenchymal Stem Cells Reduce Damage from Oxidative Stress and the Epithelial-Mesenchymal Transition in Renal Epithelial Cells Exposed to Oxalate and Calcium Oxalate Monohydrate.* Stem Cells Int, 2019. **2019**: p. 6935806.
8. Phinney, D.G. and M.F. Pittenger, *Concise Review: MSC-Derived Exosomes for Cell-Free Therapy.* Stem Cells, 2017. **35**(4): p. 851-858.

9. Zhang, Z., J. Yang, W. Yan, Y. Li, Z. Shen, and T. Asahara, *Pretreatment of Cardiac Stem Cells With Exosomes Derived From Mesenchymal Stem Cells Enhances Myocardial Repair.* J Am Heart Assoc, 2016. **5**(1).
10. Zhang, B., L. Shen, H. Shi, Z. Pan, L. Wu, Y. Yan, X. Zhang, F. Mao, H. Qian, and W. Xu, *Exosomes from Human Umbilical Cord Mesenchymal Stem Cells: Identification, Purification, and Biological Characteristics.* Stem Cells Int, 2016. **2016**: p. 1929536.
11. Sun, L., D. Li, K. Song, J. Wei, S. Yao, Z. Li, X. Su, X. Ju, L. Chao, X. Deng, B. Kong, and L. Li, *Exosomes derived from human umbilical cord mesenchymal stem cells protect against cisplatin-induced ovarian granulosa cell stress and apoptosis in vitro.* Sci Rep, 2017. **7**(1): p. 2552.
12. Zhao T, Y.Z., Liu J, Sun H, Chen Y, Tao Y, Xu W, Qian H, Yan Y, *Mesenchymal stem cell derived exosomes enhance lymphangiogenesis via exosomal transfer of Ang-2/Tie2*. 2018: bioRxiv.
13. Liu, H., X. Sun, X. Gong, and G. Wang, *Human umbilical cord mesenchymal stem cells derived exosomes exert antiapoptosis effect via activating PI3K/Akt/mTOR pathway on H9C2 cells.* J Cell Biochem, 2019. **120**(9): p. 14455-14464.
14. Zhou, X., T. Li, Y. Chen, N. Zhang, P. Wang, Y. Liang, M. Long, H. Liu, J. Mao, Q. Liu, X. Sun, and H. Chen, *Mesenchymal stem cellderived extracellular vesicles promote the in vitro proliferation and migration of breast cancer cells through the activation of the ERK pathway.* Int J Oncol, 2019. **54**(5): p. 1843-1852.
15. Wang J, H.R., Xing Q, Feng X, Jiang X, Xu Y, Wei Z, *Exosomes Derived from Umbilical Cord Mesenchymal Stem Cells Alleviate Mifepristone-Induced Human Endometrial Stromal Cell Injury.* Stem Cell International, 2020.
16. Li, T., Y. Yan, B. Wang, H. Qian, X. Zhang, L. Shen, M. Wang, Y. Zhou, W. Zhu, W. Li, and W. Xu, *Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis.* Stem Cells Dev, 2013. **22**(6): p. 845-54.
17. Li, X., L. Liu, J. Yang, Y. Yu, J. Chai, L. Wang, L. Ma, and H. Yin, *Exosome Derived From Human Umbilical Cord Mesenchymal Stem Cell Mediates MiR-181c Attenuating Burn-induced Excessive Inflammation.* EBioMedicine, 2016. **8**: p. 72-82.
18. Li, D., Q. Liu, L. Qi, X. Dai, H. Liu, and Y. Wang, *Low levels of TGF-beta1 enhance human umbilical cord-derived mesenchymal stem cell fibronectin production and extend survival time in a rat model of lipopolysaccharide-induced acute lung injury.* Mol Med Rep, 2016. **14**(2): p. 1681-92.
19. Xiong, Z.H., J. Wei, M.Q. Lu, M.Y. Jin, and H.L. Geng, *Protective effect of human umbilical cord mesenchymal stem cell exosomes on preserving the morphology and angiogenesis of placenta in rats with preeclampsia.* Biomed Pharmacother, 2018. **105**: p. 1240-1247.
20. Ding, Y., F. Cao, H. Sun, Y. Wang, S. Liu, Y. Wu, Q. Cui, W. Mei, and F. Li, *Exosomes derived from human umbilical cord mesenchymal stromal cells*

deliver exogenous miR-145-5p to inhibit pancreatic ductal adenocarcinoma progression. Cancer Lett, 2019. **442**: p. 351-361.

21. Sun, Y., H. Shi, S. Yin, C. Ji, X. Zhang, B. Zhang, P. Wu, Y. Shi, F. Mao, Y. Yan, W. Xu, and H. Qian, *Human Mesenchymal Stem Cell Derived Exosomes Alleviate Type 2 Diabetes Mellitus by Reversing Peripheral Insulin Resistance and Relieving beta-Cell Destruction.* ACS Nano, 2018. **12**(8): p. 7613-7628.
22. Kuang, M.J., Y. Huang, X.G. Zhao, R. Zhang, J.X. Ma, D.C. Wang, and X.L. Ma, *Exosomes derived from Wharton's jelly of human umbilical cord mesenchymal stem cells reduce osteocyte apoptosis in glucocorticoid-induced osteonecrosis of the femoral head in rats via the miR-21-PTEN-AKT signalling pathway.* Int J Biol Sci, 2019. **15**(9): p. 1861-1871.
23. Thomi, G., M. Joerger-Messerli, V. Haesler, L. Muri, D. Surbek, and A. Schoeberlein, *Intranasally Administered Exosomes from Umbilical Cord Stem Cells Have Preventive Neuroprotective Effects and Contribute to Functional Recovery after Perinatal Brain Injury.* Cells, 2019. **8**(8).
24. Yan, L. and X. Wu, *Exosomes produced from 3D cultures of umbilical cord mesenchymal stem cells in a hollow-fiber bioreactor show improved osteochondral regeneration activity.* Cell Biol Toxicol, 2019.
25. Shi, Y., Y. Yang, Q. Guo, Q. Gao, Y. Ding, H. Wang, W. Xu, B. Yu, M. Wang, Y. Zhao, and W. Zhu, *Exosomes Derived from Human Umbilical Cord Mesenchymal Stem Cells Promote Fibroblast-to-Myofibroblast Differentiation in Inflammatory Environments and Benefit Cardioprotective Effects.* Stem Cells Dev, 2019. **28**(12): p. 799-811.